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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/670,915	09/24/2003	Richard Daifuku	021227-000310US	6525

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EXAMINER	
KHARE, DEVESH	
ART UNIT	**PAPER NUMBER**
1623	

DATE MAILED: 11/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/670,915	DAIFUKU ET AL.	
	Examiner	Art Unit	
	Devesh Khare	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *16-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/7/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

This application claims benefit of 60/413,337 filed 09/24/2002.

In a response filed on 7/24/2006, the applicant elected Group I, claims 1-15.

Response to Election with Traverse

Applicant's election with traverse of the genus of nucleoside compounds having formula of claim 1 and a formulation thereof defined by Group I (claims 1-15) dated 07/24/2006 is acknowledged. The traversal is on the ground(s) that "prosecution of the claims of Groups I-II would not place a substantially greater burden on the examiner". This is not found persuasive because the applicants claims encompass two distinct inventions of different class and subclass: (1) the genus of nucleoside compounds having formula of claim 1 and a formulation thereof; and (2) a method for treating a viral disease by administering the effective amount of the nucleoside compounds of claim 1, which would be burdensome to the examiner because the search of product and the method of using said product is not co-extensive. The requirement is still deemed proper and is therefore made FINAL.

Claims 16-28 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

An action on the merits of claims 1-15 is contained herein below.

35 U.S.C. 112, first paragraph rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling the particular instant compounds such as 5-aza-dC and DHAdC (see Examples 1-3, 5 and 6 of the specification herein) as a potent mutagen of HIV and effective against riboviruses, does not reasonably provide enablement for any compounds encompassed by claims herein, i.e., claim 1, in particular, widely varying **R^2; R^3; and R^5-R^{22}**, having **substituted or unsubstituted alkyl, aryl, heterocycloalkyl and heteroaryl.**

The instant specification fails to provide sufficient information that would allow the skilled artisan to **fully** practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to the genus of nucleoside compounds having formula of claim 1 and a formulation thereof as discussed above in the first lack of scope of enablement rejection.

The relative skill of those in the art: The relative skill of those in the art is low.

The predictability or unpredictability and the presence or absence of working examples and the quantity of experimentation necessary as discussed below:

While a disclosure of each and every operable species claimed is not required, in patent applications containing claimed subject matter that is directed to the biotechnology, chemical

and pharmaceutical arts, where the results are unpredictable, the disclosure within the specification of a single species usually does not provide an adequate basis to support the generic claims, as more is typically required. *In re Vickers*, 61 USPQ 122, 127 (CCPA 1944). *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In the instant case, the specification, in particular, the working examples merely show that compounds *5-aza-dC and DHAdC* within the claims, and without any substitent on the base or sugar moiety *(see Examples 1-3, 5 and 6 of the specification herein) as a potent mutagen of HIV and effective against riboviruses* was tested as discussed above.

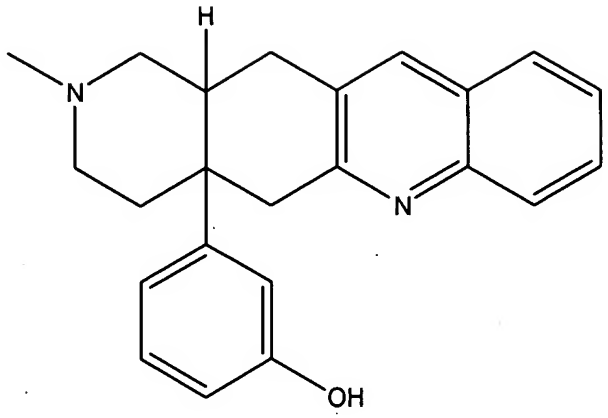
Thus, one of skill in the art would not believe that compounds *5-aza-dC and DHAdC* would have same or substantial similar physical, chemical, biological and physiological properties or activities as all other compounds encompassed by the claims in view of widely varying genus of nucleoside compounds having substituted or unsubstituted alkyl, aryl, heterocycloalkyl and heteroaryl.

The court of *In re Curtis* held that "a patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when... the evidence indicates ordinary artisans could not predict the operability .....of any other species." (see *In re Curtis* 354 F.3d 1347, 69 USPQ2d 1274, Fed. Cir. 2004).

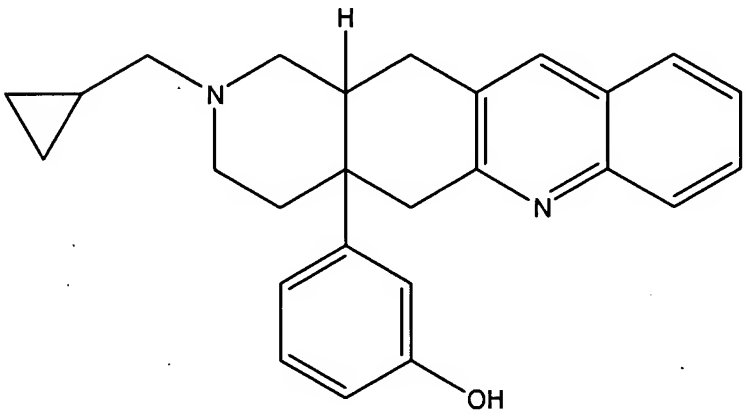
> *Drug discovery remains extremely tedious, laborious and expensive. For example, it is not all that uncommon for a pharmaceutical company to spend over one billion dollars in research and development, as well as clinical testing, before even a single drug sees the light of day in the marketplace, only then allowing said company the opportunity to begin recouping their investments for not only the successful drug, but also the countless other drugs that failed. Despite recent advancements in the sophistication of drug discovery instrumentation and techniques, an extraordinary degree of unpredictability still remains in the biotechnology, chemical and pharmaceutical arts, therefore requiring continued trial and error experimental research. The basis for the extraordinary degree of unpredictability associated with drug discovery in particular, can be attributed to the exquisite stereospecificity that exists between an enzyme and its corresponding substrate, or a ligand*

and its corresponding receptor. This principle is particularly evidenced by the following examples previously documented in the biotechnology, chemical and pharmaceutical scientific literature and prior art.

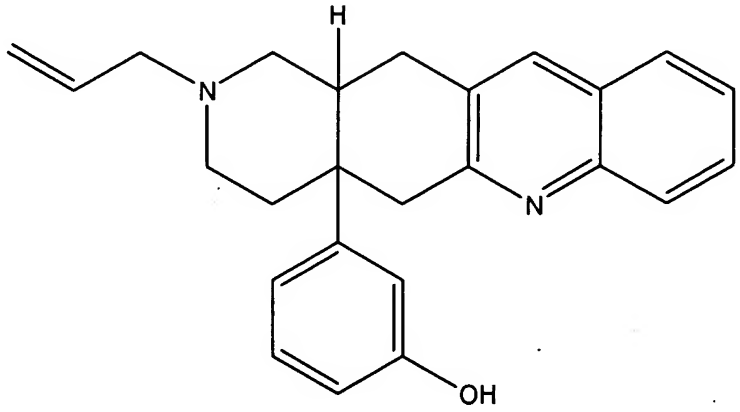
The unpredictable and surprisingly dramatic effects that can result from a simple modification of even a single pendant chemical moiety of an active core compound is strikingly apparent when considering opioid analgesics, for example. Upon simple substitution of the N-methyl group of TAN-67 (illustrated hereinbelow), which is a highly selective and potent nonpeptidic δ opioid receptor agonist, *with either a methylcyclopropyl group, or even an allyl group for that matter, TAN-67 is subsequently converted into a δ opioid receptor* antagonist! *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Ed., McGraw-Hill, NY, page 549 (1996); and Nagase, H., et al., The Pharmacological Profile of δ Opioid Receptor Ligands, (+) and (-) TAN-67 on Pain Modulation, Life Sciences, Vol. 68, pp. 2227-2231 (2001).*



3-(1,2,3,4,4a,5,12,12a-octahydro-2-methylpyrido[3,4-*b*]acridin-4a-yl)phenol (a.k.a. TAN-67)
delta opioid receptor ***agonist***

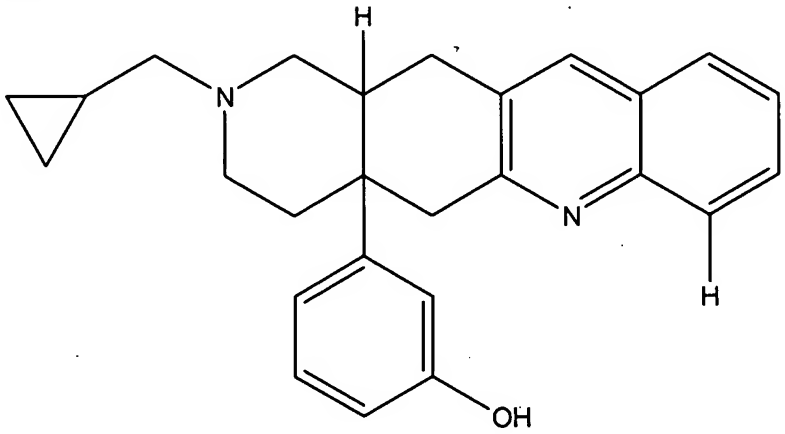


3-(2-(cyclopropylmethyl)-1,2,3,4,4a,5,12,12a-octahydropyrido[3,4-*b*]acridin-4a-yl)phenol
delta opioid receptor ***antagonist***

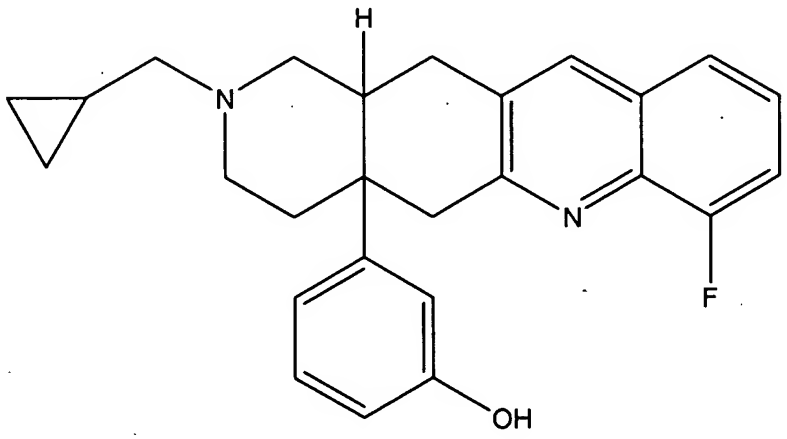


3-(2-allyl-1,2,3,4,4a,5,12,12a-octahydropyrido[3,4-*b*]acridin-4a-yl)phenol
delta opioid receptor ***antagonist***

In addition, if one were to modify the methylcyclopropyl substituted TAN-67, which is a δ opioid receptor antagonist, *by substituting a fluorine atom for a hydrogen atom on the aromatic phenyl ring near the quinoline nitrogen (illustrated hereinbelow), the δ opioid receptor* antagonist *would be converted into a* partial *δ opioid receptor* agonist, *even though fluorine and hydrogen have the same atomic radius!!*



3-(2-(cyclopropylmethyl)-1,2,3,4,4a,5,12,12a-octahydropyrido[3,4-*b*]acridin-4a-yl)phenol
delta opioid receptor ***antagonist***



3-(2-(cyclopropylmethyl)-7-fluoro-1,2,3,4,4a,5,12,12a-octahydropyrido[3,4-*b*]acridin-4a-yl)phenol
partial delta opioid receptor ***agonist***

In general, the basis for the extraordinary degree of unpredictability associated with all of the previously discussed unexpected scientific experimental results can be directly attributed to the exquisite stereospecificity that exists between an enzyme and its corresponding substrate, and a ligand and its corresponding receptor. As a result, one of ordinary skill in the art would not be able to reasonably predict or anticipate the ramifications that minor structural changes, with respect to different core compounds, can have on the bioactive properties thereof.
In this case, the compounds do not share the central and critical common core of structure in view of widely varying genus of nucleoside compounds having substituted or unsubstituted alkyl, aryl,

heterocycloalkyl and heteroaryl. Without a representative correlation between how variations in chemical structure directly impact as a potent mutagen of HIV and effective against riboviruses, *the skilled artesian would be overburdened with trying to predict, by extrapolation of only a small portion of chemical derivatives, which of the infinite number of derivatives disclosed across the entire scope of the extremely generic claims would actually exhibit* as a potent mutagen of HIV and effective against riboviruses.
In conclusion, due to the extraordinary degree of unpredictability in the art at the time the instant application was filed with respect to accurately extrapolating how minor structural changes of various chemical substituents can dramatically affect the inhibitory characteristics thereof, one of ordinary skill in the relevant art would not be able use the invention commensurate in scope with the aforementioned rejected claims.
Therefore the enabling evidence for the compounds *5-aza-dC and DHAdC* is not considered to represent each and every compound encompassed by the claims.

Thus, the specification fails to provide clear and convincing evidence in sufficient support of the broad use of any compounds recited in the instant claims. As a result, necessitating one of skill to perform an exhaustive search and **undue experimentation** for the embodiments of any compounds recited in the instant claims suitable to practice the methods of the invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation* to test all compounds encompassed in the instant claims, with no assurance of success.

35 U.S.C. 112, second paragraph rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recites the limitation "according to claim 3, wherein R^{11} is a member selected from silyl groups and substituted or unsubstituted alkyl ethers". There is insufficient antecedent basis for this limitation in the claim. There is no mention of the silyl groups and substituted or unsubstituted alkyl ethers in claim 3. Either the silyl groups and substituted or unsubstituted alkyl ethers should be recited in Claim 3 or Claim 4 should be cancelled.

35 U.S.C. 102(b) rejection

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Wierenga (US 4,140,850).

Wierenga discloses the nucleosides compounds of formula II (col.2, lines 20-30). Wierenga discloses said compounds wherein R^1 = '=O'; Y = N; R^7= alkyl; R^3= '=O'; R^8= H; Z=C; R^2= '=O'; R^{4a}= OH; R^5= OH and R^6= CH_2OH (col.2, lines 20-35) are encompassed by the applicant's compounds of claim 1.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Driscoll et al (Driscoll) (US 4,788,181).

Driscoll discloses the nucleosides compounds; see structures (col.2, lines 60-65; col.3, lines 5-10; and col.3, structure 4). Driscoll discloses said compounds wherein R^1

= NH_2; Y = N or C; R^7= alkyl or H; R^3= '=O'; R^8= H; Z=C; R^2= H; R^{4a}= H or OH; R^4= H or OH; R^5= H or OH and R^6= CH_2OH (col.2, lines 60-65; col.3, lines 5-10; and col.3, structure 4) are encompassed by the applicant's compounds of claim 1.

35 U.S.C. 103(a) rejection

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5 and 8-15 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Driscoll et al. (Driscoll) (U.S. Patent No. 4,788,181) in combinations with Wierenga (U.S. Patent 4,140,850) in view of Meyer et al. (Meyer) (U.S. Patent 5,574,142).

Like the instantly claimed invention, the Driscoll's patent teaches the cytidine and dideoxycytidine compounds and their monophosphates wherein R^1 = NH_2; Y = N or C; R^7= alkyl or H; R^3= '=O'; R^8= H; Z=C; R^2= H; R^{4a}= H or OH; R^4= H or OH; R^5= H or OH and R^6= CH_2OH (see structures in col.2, lines 60-65; col. 3-4, Scheme I, 4 & 10; col. 5, 16 & 18-21; col.6, 1 & 24; and col.7, 3 &26). The prior art discloses that said compounds are useful in the anti-viral therapy, both against RNA viruses and against DNA viruses (col.2, lines 37-39). Furthermore, Driscoll's patent discloses that any substitution on nucleoside compound such as in the structure 1 in col.6 can make the compound more susceptible to penetration of the blood-brain barrier and therefore effective against the AIDS virus in brain (col.7, lines 58-63). The Driscoll's patent also

discloses that said nucleoside compounds can be phosphorylated at the C-5' position to form nucleotides; both the unphosphorylated and the phosphorylated compounds can be administered to an infected host via orally, intravenously, or the like (col.3, lines 57-60). The prior art discloses that the lower doses of monophosphorylated nucleoside compounds can be required for the protection of HTLV-III/LAV infected cells because their triphosphate formation is facilitated when penetrated the cell membrane (col.7, lines 25-36). Therefore, with regard to claims 8 and 10 wherein C-5' is phosphorylated with the group R^6, it would be within the scope of the artisan in this art to accomplish the nucleotides of said compounds through routine experimentation by phosphorylating the C-5' position to form nucleotides because the prior art teaches that the triphosphate formation of a monophosphorylated nucleoside is facilitated when a monophosphorylated nucleoside is penetrated into the cell membrane conjugates, in the absence of unexpected results with a particular combination.

It is noted that in the compound claims 9 and 11, the recitation of an intended use such *in vivo* cleavage of said compound after entry into a cell not afforded any patentable weight.

The Wierenga's patent teaches the nucleoside compounds wherein R^1 = '=O'; Y = N; R^7= alkyl; R^3= '=O'; R^8= H; Z=C; R^2= '=O'; R^{4a}= OH; R^5= OH and R^6= CH_2OH (see structures in col.2, lines 20-30; col.5 to col. 8, Table I & II). Silicon substituted hydroxyl group of a ribose moiety is also disclosed (col.10, lines 45-55). The pharmaceutical

preparations of said compounds are useful for their activity *in vitro* against various susceptible DNA viruses (col.5, lines 1-20).

The formulation of claims 12-15 differs from the Driscoll and Wierenga's patents by claiming a formulation of nucleoside compound and a second compound A-B of claim 12. The Driscoll and Wierenga's patents teach a pharmaceutical composition of said nucleosides in the absence of a second compound A-B and a polycationic carrier. It is noted that the Driscoll patent does not teach a phosphorus moiety substituted with a linker "L".

Meyer teaches the pharmaceutical compositions containing oligonucleotides covalently linked through a peptide moiety to a carrier moiety, which facilitates delivery of said drug (col. 1, lines 5-10). Meyer discloses surfactant carriers similar to instantly claimed A-B, having a hydrophilic and a hydrophobic residue (col.4, lines 27-35 and Fig. 7). Meyer discloses a nucleotide (ODN) with a modified phosphor-di-ester group wherein the C-5' position of the nucleoside is linked to a phosphate group having an alkyl group linker (Fig.3). Meyer also discloses the use of polyamine carriers or cationic macromolecules in the composition to enhance the cellular uptake of said composition (col.4, lines 37-49). The polycationic carriers such as dendrimers are disclosed (Fig.9). Meyer discloses said composition in aqueous form for topical application (col. 19, lines 26-27).

It would have been obvious to person having ordinary skill in the art at the time the invention was made having the above-cited references before him, to select any substitution for variable $R^1 - R^{18}$ in nucleoside compounds as taught by the Driscoll and Wierenga's patents and combining with a second compound A-B and a polycationic carrier to form a formulation to enhance the cellular uptake of said composition as taught by Meyer. The motivation is provided by the Driscoll patent because Driscoll disclosed that the lower doses of said monophosphorylated nucleoside compounds are needed for the protection of HTLV-III/LAV infected cells because their triphosphate formation is facilitated when said compounds are penetrated into the cell membrane (col.7, lines 25-36).

It is noted that no prior art can be appropriately applied to the compounds of claims 6 and 7.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Devesh Khare whose telephone number is (571)272-0653. The examiner can normally be reached on Monday to Friday from 8:00 to 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anna Jiang, Supervisory Patent Examiner, Art Unit 1623 can be reached at (571)272-0627. The official fax phone numbers for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Devesh Khare, Ph.D.,J.D.
Art Unit 1623
November 13, 2006